Lifestyle and Progression of Lower Urinary Tract Symptoms in German Men-Results From the EPIC-Heidelberg Cohort

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Abstract: OBJECTIVE To examine if lower urinary tract symptom (LUTS) progression was related to anthropometric and lifestyle factors. MATERIAL AND METHODS The analysis included 5495 men who participated in the EPIC-Heidelberg cohort (recruited 1994-1998) and who reported an International Prostate Symptom Score < 8 at follow-up 4 (FUP4, 2007-2009), had not reported taking -adrenoreceptor antagonists or 5- reductase inhibitors or prostate surgery for benign prostatic hyperplasia/LUTS treatment. LUTS progression was defined as an International Prostate Symptom Score 8 at FUP5 (2010-2012). Using logistic regression analysis, education, marital status, satisfaction with life, satisfaction with health, history of diabetes and of hypertension, smoking, alcohol consumption, body mass index (BMI), waist circumference, and physical activity were examined as potential LUTS risk factors adjusting for age. RESULTS Increase in BMI between baseline and FUP4 of 2 BMI units was related to LUTS progression (odds ratio 1.30, 95% confidence interval 1.08-1.57) compared with stable BMI. Compared to men who were very satisfied with life at baseline, those who were satisfied (1.28, 1.11-1.47), unsatisfied (1.80, 1.31-2.46) or very unsatisfied with life (1.43, 0.62-3.34) were more likely to report LUTS progression. Men with longer education had higher odds of LUTS progression than men with primary education only (1.25, 1.06-1.48). Adjusting for BMI or lifestyle factors did not attenuate these associations. Smoking habits, alcohol consumption, physical activity, self-reported history of diabetes or hypertension, and marital status were not related with LUTS progression. CONCLUSION Our results confirm some, but not all previously observed risk factors for LUTS progression.

DOI: https://doi.org/10.1016/j.urology.2018.06.013

Introduction

Many men experience lower urinary tract symptoms (LUTS) as they age [1-3]. So far, however, increasing age is the only factor that is clearly related with LUTS progression, and only few studies have examined which other factors are actually associated with LUTS progression or improvements. Factors most often examined so far are obesity and physical activity [4-9], but also chronic disease conditions, smoking, alcohol consumption or education [10-13]. Results of these studies are rather heterogeneous. Obesity tends to be associated with disease progression in several, but not all [4,5,14] studies, and physical activity tends to show the opposite effect, although again the observed associations are not fully consistent [4,6,8-12].

Given the paucity of studies that addressed the question whether other factors than obesity are related to the risk of LUTS progression in elderly men, we used data of the EPIC-Heidelberg cohort. In this cohort, LUTS was assessed at two points during prospective follow-up, allowing for examining the effect of a variety of lifestyle factors on LUTS progression among middle-aged and elderly men.

Material and Methods

The EPIC study started in the early 1990s as a European initiative to examine risk factors for cancer and other chronic diseases. Participants were recruited in 10 European countries between 1994 and 1998, including more than 25,000 men and women in Heidelberg [15,16]. Men 40 to 65 years old and women aged 35 to 65 who lived in Heidelberg and surrounding municipalities were included in the cohort. At baseline, all participants filled in a lifestyle and a dietary questionnaire and provided more information during a standardized interview. Lifestyle questions included a detailed history of smoking and alcohol consumption, physical activity, medication use, and history of chronic diseases [15,17]. Body weight, height, waist and hip circumferences were measured by a trained interviewer.

In EPIC-Heidelberg, follow-up (FUP) for chronic diseases is conducted every 2-3 years [18] via questionnaire. Benign prostatic hyperplasia has not been assessed as such at baseline or during FUP

1-3, but all participants were asked to report medical diagnoses of benign tumors (including BPH) and any type of surgery, including transurethral resection of the prostate (TURP). Medication use has been assessed at baseline and all FUPs and has been coded using the ATC systematic. In our analysis, we considered the following drug groups: G04CA (α-adrenoreceptor antagonists), G04CB (5-α reductase inhibitors), and G04CX (other drugs used in BPH; this group includes plant-based and homeopathic products).

Outcome assessment: In follow-up (FUP) rounds 4 (conducted 2007-2009) and 5 (2010-2012), male study participants were asked to complete the International Prostate Symptom Score (IPSS), which assesses the frequency of the lower urinary tract symptoms "incomplete emptying"," frequency", "intermittency", "urgency", "weak stream", "straining", and "nocturia". For the first six questions (1-6) men can choose from the replies 'not at all', less than 1 in 5', 'less than half the time', 'more than half the time', or 'almost always'. Response choices for the last question (7) were 'none', '1 time', '2 times', '3 times', '4 times', '5 times or more'. A score ranging from 0 to 5 was assigned for each of the seven symptoms. A total IPSS was calculated by summing the individual scores ranging from 0-35.

In addition to the IPSS, men were asked whether a physician had (ever) diagnosed BPH (yes/no; if yes, the respective year), whether they took any BPH/LUTS medication (yes/no), including over-the-counter drugs, and whether they have had BPH surgery (yes/no; if yes, the respective year).

Study population: Of 11,928 male participants of the EPIC-Heidelberg cohort, men were eligible for our analysis if they had participated in FUP 4 and FUP 5, had not been diagnosed with prostate cancer until FUP 5, had replied to at least 4 of the 7 IPSS questions, had not reported taking α-adrenoreceptor antagonists or 5-α reductase inhibitors for treatment of BPH or LUTS up to FUP 4, and had not reported prostate surgery for BPH/LUTS treatment up to FUP 4, leaving 6,917 men. In our analysis, we only included men with IPSS ≤ 7 at FUP 4 and classified them as having "no/mild LUTS"; thus, the analytical cohort comprised 5,495 men.

Statistical analysis: LUTS progression was defined as progression from "no/mild LUTS" (IPSS ≤ 7) at FUP4 to "moderate/severe LUTS" (IPSS of 8 or higher) at FUP 5. Smoking was categorized into never, former and current smokers. Education was determined by highest degree of education and categorized into "no formal education / primary school completed", "technical/professional school completed", "secondary school", or "longer education (i.e., university degree)". Marital status was coded as "single", "married / living with a partner", "divorced / separated", or "widowed". Participants were asked at recruitment how satisfied they were with their lives and with their health, with answers categorized as “very satisfied”, “satisfied”, “unsatisfied” and “very unsatisfied”. Men were classified as having a history of hypertension or type-2 diabetes at recruitment or at FUP 4 if they replied "yes" to the question whether a doctor had ever told them that they had the respective disease. Body mass index (BMI) was computed from weight and height, measured by training study personnel at recruitment. BMI was categorized into normal (< 25 kg/m²), overweight (25- <30 kg/m²), or obese (≥ 30 kg/m²). Waist circumference is an alternative indicator of obesity, which is more specific for abdominal obesity. We divided waist circumferences into three categories: low (< 94 cm), medium (94-101 cm), and high (≥ 102 cm) [19]. At FUP 4 both BMI and waist circumference were self-reported by the study participants. Physical activity was assessed at baseline using previously established (“Cambridge”) Physical Activity Score and categorized into “active”, “moderately active”, “moderately inactive”, and “inactive” [20].

We used computed percentages and means (along with standard deviations [SD]) for descriptive analyses. To examine whether selected baseline characteristics were associated with progression of LUTS, as assessed in FUP 4, we used logistic regression models to compute odds ratios (OR) and corresponding 95% confidence intervals (CI). In all models, we adjusted for age at follow-up 4 and time difference between completion of follow-up 4 and follow-up 5. In sensitivity analyses, we used different types of adjustment, e.g. we adjusted the associations of BMI and waist circumference for smoking status, alcohol consumption, and physical activity (and vice versa); however, as the multivariate adjustments did not materially change study findings, we decided to report findings

based on the model adjusted only for age and time difference between completion of follow-up 4 and follow-up 5.

Results

Of 5,495 participants included in our analysis, 1034 (18.8%) progressed from no/mild LUTS to moderate/severe LUTS between FUP4 and FUP5 (**Table 1**). Those who progressed were almost 2 years older compared with men who did not report moderate/severe LUTS at FUP5, but did not differ strongly in mean BMI, in spite of a slightly larger waist circumference. However, men with and without progression differed with respect to self-reported diagnosis of BPH at FUP5 (31 vs. 13%) and the prevalence of BPH medication use at FUP5 (14 vs. 4%).

As expected, the odds of having first reports of moderate/severe LUTS symptoms in FUP5 increased with increasing age (**Table 2**). Obese men tended to have a higher odds of LUTS progression, which was true for obesity at baseline and obesity at FUP4, although neither OR was statistically significant. However, an increase in BMI between baseline and FUP4 of at least 2 BMI units was related to a higher odds of LUTS progression (OR = 1.30, 95% CI 1.08-1.57) compared with stable BMI during follow-up. On the other hand, there was no association between weight loss and LUTS progression. Large waist circumference at baseline was also associated with higher odds of LUTS progression (OR = 1.18, 95% CI 0.99-1.40; 102+ cm vs. < 94 cm); the association with waist circumference at FUP4 and the increase in waist circumference during follow-up was less strong.

Smoking habits, alcohol consumption and physical activity at baseline or at follow-up were not related with the odds of LUTS progression (Table 2). Compared to men who were very satisfied with their life at baseline, those who were satisfied or unsatisfied, but not those who were very unsatisfied with their life, were more likely to report LUTS progression. The same was true for satisfaction with health at baseline. Adjusting for BMI or lifestyle factors did not attenuate these associations (Supplementary Table 1). With respect to chronic disease conditions, neither self-

reported history of diabetes nor hypertension were associated with an increased odds of LUTS progression. Marital status was not related to the risk of LUTS progression. Compared with men with a primary school degree, men with longer education, e.g. a university degree, had an increased odds of LUTS progression.

Discussion

In this cohort of elderly German men, an increase in BMI, but not in waist circumference, between baseline assessment and FUP 4 was associated with LUTS progression. Being less satisfied with health and life in general was also associated with LUTS progression.

Obesity is often associated with elevated insulin concentrations, which have been hypothesized to be responsible for an obesity-LUTS association [21]. Firstly, a "trophic" effect of high insulin concentrations may induce an enlarged prostate, and men with increased prostate size are more likely to develop LUTS than men with smaller prostate size [22]. Secondly, an increased insulin concentration is also associated with an increased sympathetic nerve activity, which increases smooth muscle activity of the prostate and may further contribute to LUTS symptoms [21]. Several previous studies examined obesity as a factor for LUTS progression (see supplementary Table 2). While study designs and definitions of LUTS or PBH progression differed, most studies observed associations between obesity and LUTS progression irrespective of the outcome's definition. Although in our analysis high BMI at baseline or at FUP 4 were not statistically significantly associated with a higher odds of LUTS progression, the increase in BMI over a period of 10-14 years (between baseline and FUP 4) was related to a 30% higher odds of having moderate/severe LUTS at FUP5. In contrast, we observed no strong association between increase in waist circumference over time and LUTS progression. In the Prostate Cancer Prevention Trial (PCPT), higher WHR was associated with increased risk of total (defined as treatment of LUTS or IPSS > 14 assessed twice) and severe (treatment or IPSS > 20 twice) incident BPH [9]. In the "Osteoporotic Fractures in Men (MrOS)" study, overweight and obese men had

a higher risk of developing LUTS [6]. In that study, LUTS was defined as IPSS ≥ 8, medication use, or surgery. In another analysis of the MrOS study, in which LUTS progression was determined with group-based trajectory modeling of the IPSS measures, overweight and obesity were also related to LUTS progression [11]. In the Health Professionals Follow-up Study (HPFS) [7], higher BMI and greater WC were statistically significantly associated with incidence of moderate or worse LUTS (IPSS >=14) or progression to severe LUTS (IPSS ≥ 20). In an Australian study, greater abdominal fat mass was related to progression of "storage" symptoms of LUTS [10]. In the Olmsted County Study [5], in which LUTS progression was defined as progression to IPSS ≥ 8 or an increase of at least 4 points, weight change was not related to LUTS progression, and no association of BMI or waist circumference with LUTS progression (an increase of 8+ points in the IPSS during the 3-year follow-up period) was observed in a small Korean study [4].

Physical activity at baseline showed a suggestive, but statistically non-significantly inverse associated with LUTS progression in our cohort. Two studies reported protective effects of physical activity on LUTS progression [6,10], but most studies did not see such effects in middle-aged/elderly men [4,8,9,11,12].

We observed no associations of smoking or alcohol consumption with LUTS progression. Previous studies that examined these two lifestyle factors reported mixed results (alcohol no association [4,11] or positive association [12]; smoking no association [9,11,12] or positive association [4]). As in our study, previous studies did not report associations between history of chronic diseases such as hypertension (no association [11] and type-2 diabetes (no association [4,9,11] and risk of LUTS progression, although a number of studies reported positive associations between hypertension and type-2 diabetes and risk of LUTS or BPH cross-sectionally [23].

Education was not consistently related with LUTS progression in our analysis, confirming the result of one US study [6], whereas a second US study reported that men with lower education had a higher risk of LUTS progression [13].

The only factors that were related to LUTS progression in our study - in addition to weight gain - were satisfaction with health and with life in general. This has not been reported before, but numerous studies have previously shown that the simple questions of how satisfied somebody is with his life or his health is a very good prognostic factor for morbidity and mortality, years and even decades after this question has been asked [24]. We excluded men with moderate/severe LUTS at FUP 4 and men with a diagnosis of LUTS or BPH from the analysis and, thus, pre-existing LUTS is not likely to have influenced self-rated health or satisfaction with life. Also, overweight or obese men did not have lower satisfaction with health or life than lean men in our analysis (results not shown). It is interesting to note that men who were very unsatisfied with health or life were not more likely to report LUTS progression. It has been shown that LUTS and BPH affect quality of life [25], but further prospective research is warranted to address the opposite question.

A strength of our study is the rather large sample size of middle-aged and elderly men from the general population. Several potential risk factors were assessed at baseline and at FUP4, which allowed us for comparing the importance of risk factors depending on lag time. However, BMI and waist circumference were assessed differently at baseline (measured at the recruitment center) and at FUP4 (self-reported). Similarly, chronic diseases such as hypertension and type-2 diabetes were self-reported and have not been verified (besides type-2 diabetes at FUP4) by trained personnel. Also, the report of BPH and TURP has usually not been verified by a trained physician unless information showed up during verification of cancer.

In conclusion, we confirm an effect of weight gain on the progression of LUTS in middle-aged and elderly men, but other factors of the metabolic syndrome, namely a history of type-2 diabetes and hypertension, which have previously been associated with LUTS progression in other cohorts, were not associated. The differences in the definition of LUTS progression made it difficult to compare results between studies directly and might explain the heterogeneity of findings across different studies.

References

1. Haidinger G, Waldhor T, Madersbacher S, Schatzl G and Vutuc C: Prevalence of lower urinary tract symptoms in Austrian males: update 2009. Urol Int. 87: 385-91, 2011.
2. Robert G, Descazeaud A, Azzouzi R, Saussine C, Haillot O, Dumonceau O, Ballereau C, Fourmarier M, Devonec M, Lukacs B *et al.*: Impact of lower urinary tract symptoms on discomfort in men aged between 50 and 80 years. Urol Int. 84: 424-9, 2010.
3. Boyle P, Robertson C, Mazzetta C, Keech M, Hobbs FD, Fourcade R, Kiemeney L and Lee C: The prevalence of lower urinary tract symptoms in men and women in four centres. The UrEpik study. BJU Int. 92: 409-14, 2003.
4. Choo MS, Han JH, Shin TY, Ko K, Lee WK, Cho ST, Lee SK and Lee SH: Alcohol, Smoking, Physical Activity, Protein, and Lower Urinary Tract Symptoms: Prospective Longitudinal Cohort. Int Neurourol J. 19: 197-206, 2015.
5. St Sauver JL, Sarma AV, Hollingsworth JM, Jacobson DJ, McGree ME, Dunn RL, Lieber MM and Jacobsen SJ: Associations between modest weight changes and onset and progression of lower urinary tract symptoms in two population-based cohorts. Urology. 78: 437-41, 2011.
6. Parsons JK, Messer K, White M, Barrett-Connor E, Bauer DC and Marshall LM: Obesity increases and physical activity decreases lower urinary tract symptom risk in older men: the Osteoporotic Fractures in Men study. Eur Urol. 60: 1173-80, 2011.
7. Mondul AM, Giovannucci E and Platz EA: A prospective study of obesity, and the incidence and progression of lower urinary tract symptoms. J Urol. 191: 715-21, 2014.
8. Penson DF, Munro HM, Signorello LB, Blot WJ and Fowke JH: Obesity, physical activity and lower urinary tract symptoms: results from the Southern Community Cohort Study. J Urol. 186: 2316-22, 2011.
9. Kristal AR, Arnold KB, Schenk JM, Neuhouser ML, Weiss N, Goodman P, Antvelink CM, Penson DF and Thompson IM: Race/ethnicity, obesity, health related behaviors and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. J Urol. 177: 1395-400; quiz 1591, 2007.
10. Martin S, Lange K, Haren MT, Taylor AW and Wittert G: Risk factors for progression or improvement of lower urinary tract symptoms in a prospective cohort of men. J Urol. 191: 130-7, 2014.
11. Marshall LM, Holton KF, Parsons JK, Lapidus JA, Ramsey K and Barrett-Connor E: Lifestyle and health factors associated with progressing and remitting trajectories of untreated lower urinary tract symptoms among elderly men. Prostate Cancer Prostatic Dis. 17: 265-72, 2014.
12. Maserejian NN, Kupelian V, Miyasato G, McVary KT and McKinlay JB: Are physical activity, smoking and alcohol consumption associated with lower urinary tract symptoms in men or women? Results from a population based observational study. J Urol. 188: 490-5, 2012.
13. Fowke JH, Munro H, Signorello LB, Blot WJ and Penson DF: Association between socioeconomic status (SES) and lower urinary tract symptom (LUTS) severity among black and white men. J Gen Intern Med. 26: 1305-10, 2011.
14. Burke JP, Rhodes T, Jacobson DJ, McGree ME, Roberts RO, Girman CJ, Lieber MM and Jacobsen SJ: Association of anthropometric measures with the presence and progression of benign prostatic hyperplasia. Am J Epidemiol. 164: 41-6, 2006.
15. Boeing H, Wahrendorf J and Becker N: EPIC-Germany--A source for studies into diet and risk of chronic diseases. European Investigation into Cancer and Nutrition. Ann Nutr Metab. 43: 195-204, 1999.
16. Riboli E and Kaaks R: The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol. 26 Suppl 1: S6-14, 1997.
17. Boeing H, Korfmann A and Bergmann MM: Recruitment procedures of EPIC-Germany. European Investigation into Cancer and Nutrition. Ann Nutr Metab. 43: 205-15, 1999.
18. Bergmann MM, Bussas U and Boeing H: Follow-up procedures in EPIC-Germany--data quality aspects. European Prospective Investigation into Cancer and Nutrition. Ann Nutr Metab. 43: 225-34, 1999.

19. Lean ME, Han TS and Morrison CE: Waist circumference as a measure for indicating need for weight management. BMJ. 311: 158-61, 1995.
20. Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S and Day NE: Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr. 6: 407-13, 2003.
21. Hammarsten J and Hogstedt B: Hyperinsulinaemia as a risk factor for developing benign prostatic hyperplasia. Eur Urol. 39: 151-8, 2001.
22. Simon RM, Howard LE, Moreira DM, Roehrborn C, Vidal AC, Castro-Santamaria R and Freedland SJ: Does Prostate Size Predict the Development of Incident Lower Urinary Tract Symptoms in Men with Mild to No Current Symptoms? Results from the REDUCE Trial. Eur Urol, 2015.
23. Vignozzi L, Gacci M and Maggi M: Lower urinary tract symptoms, benign prostatic hyperplasia and metabolic syndrome. Nat Rev Urol. advance online publication, 2016.
24. Bopp M, Braun J, Gutzwiller F and Faeh D: Health risk or resource? Gradual and independent association between self-rated health and mortality persists over 30 years. PLoS One. 7: e30795, 2012.
25. Nuotio M, Tammela TL, Luukkaala T and Jylha M: Association of urgency symptoms with self-rated health, mood and functioning in an older population. Aging Clin Exp Res. 19: 465-71, 2007.

Table 1. Selected characteristics of men with and without progression from no/mild LUTS to moderate/severe LUTS between follow-up 4 and follow-up 5, EPIC-Heidelberg

	no progression	progression
Participants (N)	4461	1034
	Mean (± SD)	Mean (± SD)
Age at recruitment (years)	50.4 (± 6.8)	52.2 (± 6.8)
BMI at recruitment (kg/m^2)	26.7 (± 3.5)	27.0 (± 3.5)
BMI at F4 (kg/m^2)	27.0 (± 3.7)	27.3 (± 3.8)
Change in BMI (kg/m^2)	0.4 (± 1.9)	0.4 (± 2.0)
Waist circumference at recruitment (cm)	94.9 (± 9.8)	95.9 (± 9.8)
Waist circumference at F4 (cm)	99.6 (± 10.6)	100.9 (± 11.0)
Change in waist circumference (cm)	4.9 (± 7.7)	5.1 (± 7.7)
	N (%)	N (%)
BPH diagnosis between F4 and F5	570 (13)	319 (31)
BPH surgery between F4 and F5	28 (1)	8 (1)
Reported use of any BPH medication at F5	192 (4)	148 (14)
Reported use of α-adrenoreceptor antagonists and 5-α reductase inhibitors at F5	77 (2)	70 (7)

SD, standard deviation; F4, follow-up 4; F5, follow-up 5

Supplementary Table 1. Results of previous studies on LUTS progression risk factors

Author	Country	Sample size	Age	Assessment	Follow-up	LUTS progression definition	Exposure	OR (95% CI)
Burke 2006	Olmsted County	2063	40-79	AUA SI	12 years	AUA SI* slope, >80th percentile	BMI 25-29.9 vs. <25 kg/m^2	0.96 (0.69-1.33)
							≥ 30 vs. <25 kg/m^2	1.04 (0.73-1.48)
							WC 95–101 vs < 95 cm	0.99 (0.70-1.38)
							WC 102–109 vs < 95 cm	0.84 (0.59-1.19)
							WC >109 vs < 95 cm	1.11 (0.79-1.56)
Kristal 2007	PCPT	5,667 (placebo arm; free of BPH at baseline)	≥ 55	IPSS	7 years	treatment or report of 2 IPSS values > 14	Light PA vs sedentary	0.92 (0.77-1.09)
							Moderate PA vs sedentary	0.93 (0.78-1.12)
							High PA vs sedentary	1.01 (0.79-1.28)
							current vs non smk	1.01 (0.81-1.27)
							Diabetes	0.87 (0.66-1.15)
							weight per 5 kg	1.02 (1.00-1.05)
							BMI 25-29 vs < 25 kg/m^2	**1.26 (1.08-1.47)**
							BMI 30-34 vs < 25 kg/m^2	**1.30 (1.08-1.57)**
							BMI ≥ 35 vs < 25 kg/m^2	1.22 (0.92-1.62)
							WHR 0.95-0.99 vs < 0.95	1.02 (0.88-1.18)
							WHR 1.00-1.04 vs < 0.95	1.16 (0.98-1.38)
							WHR ≥ 1.05 vs < 0.95	1.30 (0.95-1.78)
Parsons 2011	MrOS	1695	≥ 65	AUA SI	mean 4.6 years	AUA SI ≥ 8; documented current use of prescription medications (α-adrenergic blockers, urinary antispasmodics, and 5α-reductase	Some college or college degree vs high school or less	0.99 (0.75-1.31)
							Some grad. school or grad. school degree vs high school or less	0.87 (0.65-1.18)
							BMI 25–29.9 vs < 25 kg/m^2	**1.29 (1.00-1.68)**
							BMI ≥ 30 kg/m^2 vs < 25 kg/m^2	**1.40 (1.02-1.91)**
							Daily walking	**0.80 (0.65-0.98)**

						inhibitors for urinary symptoms) or self-report of past use of prescription medications or non-cancer prostate surgery		
St. Sauver 2011	Olmsted County (OCS) & Flint Men's Health Study	1842	70-79	AUA SI	4 years	AUA SI > 7 (OCS only)	Gained < 5% of baseline weight vs none	0.99 (0.75-1.31)
							Gained ≥ 5% of baseline weight vs none	1.05 (0.80-1.38)
						4-point Increase in AUA SI (OCS only)	Gained < 5% of baseline weight vs none	0.99 (0.80-1.22)
							Gained ≥ 5% of baseline weight vs none	1.01 (0.83-1.24)
Penson 2011	US	7318	40-79	IPSS	5 years	AUA SI > 7	25–29.9 vs. 18.5-24.9 kg/m^2	**1.13 (1.00-1.28)**
							30–34.9 vs. 18.5-24.9 kg/m^2	1.05 (0.91-1.22)
							≥ 35 vs 18.5-24.9 kg/m^2	**1.34 (1.13-1.58)**
							PA (MET hrs/day) Q1 vs Q4	**1.14 (0.99-1.32)**
							PA (MET hrs/day) Q2 vs Q4	0.96 (0.83-1.11)
							PA (MET hrs/day) Q3 vs Q4	1.04 (0.90-1.20)
Fowke 2011	US	6676	40-79	IPSS	5 years	AUA SI > 7	Some college vs college or more	**1.26 (1.07-1.49)**
							High school vs college or more	**1.28 (1.10-1.49)**
							9-11 yrs vs college or more	**1.59 (1.33-1.91)**
							< 9 yrs vs college or more	**1.48 (1.17-1.88)**
Maserejian 2012	BACH	1610	30-79 at baseline	AUASI	5-year fup	AUA SI ≥ 8	medium vs low PA	1.12 (0.60-2.11)
							high vs low PA	0.72 (0.35-1.52)

							former vs never smoking	0.91 (0.51-1.63)
							current vs never smoking	1.01 (0.55-1.84)
							0.1-1 vs 0 alcoholic drinks	**2.42 (1.24-4.75)**
							>1 vs 0 alcoholic drinks	1.73 (0.87-3.43)
Mondul 2014	HPFS	18055	40-75	AUASI	16 years	incidence of moderate or worse LUTS (IPSS ≥ 15)	BMI 25-27.5 vs 21-23 kg/m^2	**1.11 (1.02-1.21)**
							BMI ≥ 35 vs 21-23 kg/m^2	**1.61 (1.31-1.99)**
							WC 38-40 vs ≤ 33 inches	**1.23 (1.05-1.43)**
							WC > 42 vs ≤ 33 inches	**1.39 (1.19-1.63)**
							Weight gain 50 pounds vs +/- 10 since age 21	**1.31 (1.17-1.46)**
Marshall 2014	Mr OS	1740	≥ 65	AUA SI	6 years	AUA SI progressing trajectory among those with AUA SI < 8 at baseline	overweight/obese	1.7 (1.0-2.8)
							no daily walking for exercise	1.4 (0.9-2.2)
							smoking	no sign. association
							alcohol	no sign. association
							diabetes	no sign. association
							hypertension	no sign. association
Choo 2015	Korea	224	≥ 45	IPSS	3-year follow-up	increase of ≥8 points	Body mass index	1.12 (0.88-1.42)
							Waist	0.92 (0.84-1.01)
							Diabetes mellitus	1.54 (0.51-4.58)
							Alcohol	1.01 (0.42-2.41)
							Smoking	**3.08 (1.13-8.36)**
							Leisure-time PA	1.41 (0.63-3.12)

BMI, body mass index; PA, physical activity; WC, waist circumference; WHR, waist-to-hip ratio

Table 2. Association between lifestyle and social variables and progression of no/mild LUTS to moderate/severe LUTS between follow-up 4 and follow-up 5, EPIC-Heidelberg

Variable	Unit/category	Baseline information OR (95% CI)	Information at F4 OR (95% CI)
Age	years	1.04 (1.03-1.05)	
BMI	< 25 kg/m^2	1.00 (ref.)	1.00 (ref.)
	25 - 29.9 kg/m^2	1.07 (0.92-1.25)	1.00 (0.85-1.17)
	30+ kg/m^2	1.16 (0.94-1.42)	1.20 (0.99-1.46)
BMI change between baseline and follow-up 4	Decrease > 2 kg/m^2		0.90 (0.70-1.16)
	Stable		1.00 (ref.)
	Increase > 2 kg/m^2		1.30 (1.08-1.57)
Waist circumference	< 94 cm	1.00 (ref.)	1.00 (ref.)
	94 - < 102 cm	1.01 (0.86-1.19)	0.96 (0.81-1.15)
	102+ cm	1.18 (0.99-1.40)	1.13 (0.96-1.33)
Waist circumference change between baseline and follow-up 4	Decrease > 5 cm		0.92 (0.74-1.13)
	Stable		1.00 (ref.)
	Increase > 5 cm		1.04 (0.89-1.20)
Smoking habits	Never	1.00 (ref.)	1.00 (ref.)
	Former	1.00 (0.86-1.17)	1.00 (0.86-1.16)
	Current	0.93 (0.77-1.12)	0.86 (0.69-1.07)
Physical activity**	Inactive	1.00 (ref.)	
	Moderately inactive	0.92 (0.71-1.19)	
	Moderately active	0.91 (0.70-1.18)	
	active	0.85 (0.65-1.10)	
Alcohol consumption	No	0.41 (0.12-1.34)	0.44 (0.14-1.46)
	Former	1.14 (0.77-1.67)	0.88 (0.69-1.13)
	Current	1.00 (ref.)	1.00 (ref.)
Satisfaction with life**	Very satisfied	1.00 (ref.)	
	Satisfied	1.28 (1.11-1.47)	
	Unsatisfied	1.80 (1.31-2.46)	
	Very unsatisfied	1.43 (0.62-3.34)	
Satisfaction with health**	Very satisfied	1.00 (ref.)	
	Satisfied	1.31 (1.13-1.53)	
	Unsatisfied	1.51 (1.20-1.92)	
	Very unsatisfied	0.89 (0.45-1.76)	
Diabetes	Yes	1.14 (0.79-1.65)	0.98 (0.77-1.25)
Hypertension	Yes	1.07 (0.92-1.24)	0.98 (0.84-1.13)
Marital status	Single	1.00 (ref.)	1.00 (ref.)
	Married	1.03 (0.79-1.35)	1.10 (0.82-1.47)
	Divorced	0.94 (0.65-1.36)	1.12 (0.77-1.63)
	Widowed	0.56 (0.24-1.29)	1.15 (0.71-1.86)
Education**	No formal degree	1.89 (0.57-6.26)	
	Primary school	1.00 (ref.)	
	Techn./prof. school	0.98 (0.81-1.18)	
	Secondary school	1.17 (0.86-1.59)	

Longer education	1.25 (1.06-1.48)

* adjusted for age at follow-up 4 and time between follow-ups 4 and 5 (both continuous); changes in BMI and waist circumference are adjusted for BMI at baseline and waist circumference at baseline, respectively

** not assessed at follow-up 4